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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,355	06/12/2006	Robert C. Leif	90274U	8971

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EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
01/18/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,355	LEIF ET AL.	
	Examiner	Art Unit	
	MELISSA PERREIRA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-6 and 8-18* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-6,8,9 and 11-18* is/are rejected.

8)☒ Claim(s) *10* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Previous Objections/Rejections Status

1. Claims 1-6 and 8-18 are pending in the application

2. The rejection of claims 1-4,6,16 and 17 under 35 U.S.C. 102(b) as being anticipated by Leif et al. (US 6,340,744B1) is withdrawn.

3. The rejection of claims 1-4,6,16 and 17 under 35 U.S.C. 102(b) as being anticipated by Leif et al. (US 6,750,005B2) is withdrawn.

4. The rejection of claims 1-6 and 16-18 under 35 U.S.C. 103(a) as being unpatentable over Leif et al. (US 6,340,744 B1) in view of Mathis et al. (US 4,927,923) is withdrawn.

5. The rejection of claims 1-6 and 16-18 under 35 U.S.C. 103(a) as being unpatentable over Leif et al. (US 6,750,005B2) in view of Mathis et al. (US 4,927,923) is withdrawn.

6. The rejection of claims 8,9 and 11-13 under 35 U.S.C. 103(a) as being unpatentable over Xu (US 5,316,909) in view of Leif et al. (US 6,750,005B2) is withdrawn.

7. The rejection of claims 14 and 15 under 35 U.S.C. 103(a) as being unpatentable over Vallarino et al. (US 5,696,240) in view of Xu (US 5,316,909) and in further view of Leif et al. (US 6,750,005B2) is withdrawn.

Response to Arguments

8. Applicant's arguments with respect to claims 1-6 and 8-18 have been considered but are moot in view of the new ground(s) of rejection.

New Grounds of Rejection

Claim Objections

9. Claim 9 is objected to because of the following informalities: the instant claim recites “melion” which is believed to be a typographical error. Appropriate correction is required.

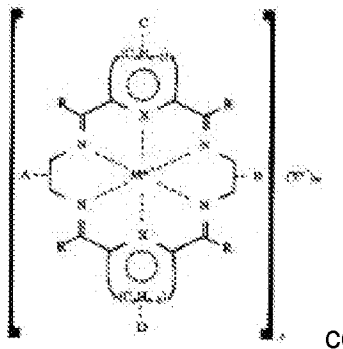
Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-4,6,8,9 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Vallarino et al. (US 5,696,240).

12. Vallarino et al. (US 5,696,240) teaches of macrocyclic complexes used for the method of analysis of a sample containing an analyte. The complexes



comprise M = metal ion selected from the group consisting of a lanthanide having an atomic number 59-71, an actinide having atomic number 89-103, etc.; R is hydrogen, straight-chain alkyl, etc.; X is selected from the group consisting of nitrogen, sulfur and oxygen which forms a part of a ring structure selected from the group consisting of pyridine, etc.; n is 2 or 3; Y is a negatively charged ion; m is the ionic charge of the metal ion in the macrocyclic complex; y^- is the ionic charge of the counterion in the macrocyclic complex; A,B,C and D are selected substituents selected from the group consisting of hydrogen, straight-chain alkyl, etc. (column 8, lines 32+; column 9; column 11, lines 1+; claim 4). The macrocyclic complexes are further conjugated to biologically active molecules to bind only to an analyte of interest and may be used in analytical procedures, e.g. fluorescent immunoassays, etc. or an injectable solution for administration to a recipient for in vivo observation and/or labeling of a target tissue (column 12, lines 45-62; column 13, lines 1-15; column 19, lines 4-48). The macrocyclic complex may comprise a solid crystalline product that have increased solubility, greater stability, etc. (column 10, lines 37-52; column 13, lines 40-54; column 23, lines 55+).

13. The complexes have emissions approximately 615 nm and 680 nm for europium(III) and approximately 545 nm for terbium and possess a long-lived

fluorescence intensity that can be substantially increased by interaction with a suitable enhancer, such as acetylacetonate, etc. (column 8, lines 31-50; column 22, lines 53+; column 23, lines 1-20 and 53+; example XXI, example XXII; column 44, lines 9-28). The enhancer, e.g. acetylacetone anticipates the organic ligand fluorophores and/or lumiphores of the instant claims as evidenced by the specification p43, lines 5+ which states that beta-diketones are particularly preferred fluorophores and lumiphores. The beta-diketones and the complexes provide a cofluorescence effect wherein the ligand absorbs the excitation energy. The cofluorescence is based on an intermolecular energy transfer that occurs from the chelate of the ion increasing fluorescence, the energy donor, to the chelate of the fluorescent ion, the energy acceptor (column 4, lines 17-39). Therefore, the complexes do not comprise a micellar solution.

14. Europium-macrocyclic complexes are coupled to agarose beads for solid phase immunoassays wherein the biotinylated agarose beads are washed and treated/incubated with the europium-macrocycle-coupled avidin solution and then centrifuged and washed thoroughly to generate the solid europium-avidin/biotinylated beads. The europium(III)-macrocycle-streptavidin complex (solid) was treated with a saturated solution of 4,4,4-Trifluoro-1-(2-thienyl)butane-1-3-dione (thenoyltrifluoroacetylacetone) in the tricine buffer and the mixture irradiated with UV light of 350-360 nm to give an intense red luminescence (example XXIX, especially step 3). Europium(III) macrocyclic complexes are mixed with an enhancer and then combined with a sample and exposed to uv light excitation at 350-385 nm (Example XXXIV; Example XXXV).

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 1-6,8,9,11,14,15 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vallarino et al. (US 5,696,240) in view of Mathis et al. (US 4,927,923).

17. Vallarino et al. (US 5,696,240) discloses macrocyclic complexes (below) for the method of analysis of a sample containing an analyte. The complexes comprise M is a metal ion selected from the group consisting of a lanthanide having an atomic number 59-71, an actinide having atomic number 89-103, etc.; R is hydrogen, straight-chain alkyl, etc.; X is selected from the group consisting of nitrogen, sulfur and oxygen which forms a part of a ring structure selected from the group consisting of pyridine, etc.; n is 2 or 3; Y is a negatively charged ion; m is the ionic charge of the metal ion in the macrocyclic complex; y^- is the ionic charge of the counterion in the macrocyclic complex; A,B,C and D are selected substituents selected from the group consisting of hydrogen, straight-chain alkyl, etc. as well as that stated above.

18. Vallarino et al. does not explicitly disclose a single-phase solution and does not disclose a cryptate.

19. Mathis et al. (US 4,927,923) discloses macropolycyclic rare earth complexes, namely cryptates complexed to a rare earth ion wherein the macropolycyclic rare earth complexes are useful as fluorescent tracers for biological substances in immunological detection or determination techniques using fluorescence. The methods of determination are in homogeneous phases or in a solid phase (column 15, lines 58+; column 16, lines 1-11). The complexes are stable in aqueous media and have excellent selectivity and stability (column 3, lines 63+; column 4; column 7, lines13-25). The excitation of the cryptate rare earth complexes enhances the fluorescence characteristics of a rare earth ion as excitation of an isolated rare earth ion produces only a very weak fluorescence because they generally have low molar absorption coefficients e (abstract; column 3, lines +; column 4, lines 1-37).

20. At the time of the invention it would have been obvious to one ordinarily skilled in the art that the cofluorescent complexes of Vallarino et al. are single-phase as the complexes of Vallarino et al. do not comprise a surfactant.

21. At the time of the invention it would have been obvious to one ordinarily skilled in the art to substitute the cryptate of Mathis et al. for the macrocyclic chelator of Vallarino et al. as both compositions can be used in the solid phase to examine the enhancement of the fluorescence of the luminescent compositions for determination techniques as excitation of the cryptate rare earth complexes enhances the fluorescence characteristics of a rare earth ion which generally have low molar absorption coefficients e. It is obvious to those skilled in the art to make known substitutions on compounds that are similar in structure and function, such as macrocyclic chelators to observe the

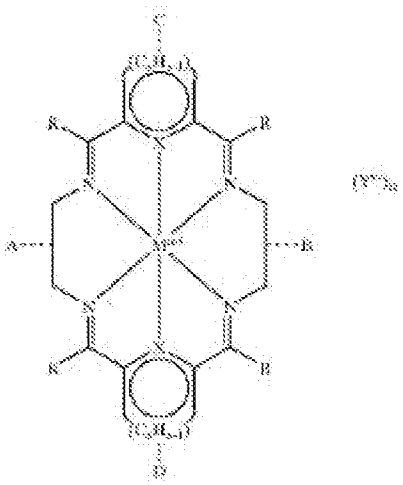
effects on the function of such compounds and to use the observations/data to further manipulate a compound to generate the desired effect, such as enhanced fluorescence.

22. Claims 1-4,6,8,9 and 11-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vallarino et al. (US 5,696,240) in view of Leif et al. (US 6,750,005B2) and in further view of Xu (US 5,316,909).

23. Vallarino et al. (US 5,696,240) discloses macrocyclic complexes (below) for the method of analysis of a sample containing an analyte. The complexes comprise M is a metal ion selected from the group consisting of a lanthanide having an atomic number 59-71, an actinide having atomic number 89-103, etc.; R is hydrogen, straight-chain alkyl, etc.; X is selected from the group consisting of nitrogen, sulfur and oxygen which forms a part of a ring structure selected from the group consisting of pyridine, etc.; n is 2 or 3; Y is a negatively charged ion; m is the ionic charge of the metal ion in the macrocyclic complex; y^- is the ionic charge of the counterion in the macrocyclic complex; A,B,C and D are selected substituents selected from the group consisting of hydrogen, straight-chain alkyl, etc. as well as that stated above.

24. Vallarino et al. does not explicitly disclose a.) a single-phase solution; and does not disclose b.) a gadolinium(III) fluorophore or lumiphore energy transfer donor compound, such as a complex of gadolinium (III) or an ionic compound of gadolinium (III); or c.) the concentration of the energy transfer donor species of claim 13.

25. Leif et al. (US 6,750,005B2) discloses a spectrofluorimetrically detectable luminescent composition comprising at least one energy transfer acceptor lanthanide element macrocycle compound having an emission spectrum peak in the range from



500 to 950 nm, , and a luminescence-enhancing amount of at least one energy transfer donor compound of yttrium or a 3-valent lanthanide element having atomic number 59-71, such as Gd, provided that the lanthanide element of said macrocycle compound and the lanthanide element of said energy transfer donor compound are not identical. M is a metal ion selected from the group consisting of a lanthanide having atomic number 57-71, etc.; R is a substituent selected from the group consisting of hydrogen, etc.; X is selected from the group consisting of nitrogen, etc.; n is 2 or 3; Y is a negatively charged ion, including acetate, etc.; m is the ionic charge of the metal ion in the macrocyclic complex; y is the ionic charge of the counterion in the macrocylic complex; A,B,C and D are selected substituents selected from the group consisting of hydrogen, straight-chain alkyl, etc. The luminescent compositions can be functionalized wherein the macrocycles are substituted with reactive functional groups

at which reaction with analytes can take place (column 2, lines 18+; column 3, lines 45+; column 4; column 7).

26. A method for analysis of a sample suspected of containing at least one analyte is provided and comprises:

27. a.) contacting said sample with the complex of the disclosure, etc.; b.) adding to the reaction medium a luminescence-enhancing amount of at least one energy transfer donor compound of yttrium, etc.; c.) subjecting the reaction mixture to excitation energy in the range of 200-400 nm, whereby enhanced luminescence in the range of 500-950 nm is generated; d.) monitoring the luminescence of the reaction medium for at least one of the following: 1.) presence and/or concentration of said conjugate; 2.) presence and/or concentration of the product of the interaction of said complex with said binding material; and 3.) presence and/or concentration of the product of the interaction of the conjugate with the binding material (column 2, lines 55+; column 3, lines 1-20).

28. The concentration of the energy transfer donor compound is present in a concentration greater than the concentration of the energy transfer acceptor macrocycle, such as a range from 1×10^{-5} to 1×10^{-3} moles per liter and provides for cofluorescence (column 9, lines 47-51; column 18, lines 1-8).

29. The luminescent compositions comprise a micelle-producing amount of least one surfactant (column 10).

30. The Eu-Macrocycle-Avidin conjugates are attached to agarose beads for solid state luminescence studies and therefore the Eu-Macrocycle-Avidin conjugates are solid (examples IV, VIII).

31. Xu (US 5,316,909) discloses lanthanide chelates (e.g. europium, terbium, etc.) for fluorescence measurement wherein a chelate of a fluorescence-increasing ion (e.g. lanthanides and yttrium) or compound (e.g. thenoyltrifluoroacetone, etc.) is incorporated to bring about a cofluorescence effect (internal fluorescence effect). The fluorescence intensity of the lanthanide chelate is thereby enhanced when biological active substances are measured (abstract; column 2, lines 33+; column 3; column 4, lines 12-21; table 1). Xu states that most of the cofluorescence complexes comprise a detergent (surfactant) to form micelles and therefore not all of the cofluorescence complexes require a detergent (surfactant) (column 4, lines 22-32).

32. Biological substances can be labeled directly with very strong fluorescent particles by using a chemical bond or adsorption. After the immunochemical reaction the fluorescence of the particles is measured either in suspension or directly on the surface of a solid support (column 4, lines 33+; column 5, lines 1-9).

33. At the time of the invention it would have been obvious to one ordinarily skilled in the art that the cofluorescent complexes of Vallarino et al. are single-phase as Xu teaches that cofluorescent complexes comprising an enhancing agent (e.g. lanthanide chelate or beta-diketone) do not necessarily require a detergent (surfactant) to generate complexes for solid state luminescence and the complexes of Vallarino et al. do not comprise a surfactant.

34. At the time of the invention it would have been obvious to one ordinarily skilled in the art to substitute the energy transfer donor compound, such as beta-diketone of Vallarino et al. for the Gd energy transfer donor compound of Leif et al. as Xu teaches

that both lanthanides or compounds (e.g. thenoyltrifluoroacetone) are acceptable energy transfer donor compounds for cofluorescent complexes, such as that of Vallarino et al. Vallarino et al. teaches of the use of beta-diketone energy transfer donor compounds (i.e. enhancers) and thus the substitution of one equivalent energy transfer donor compound for another energy transfer donor compound is predictable and provides for the advantage of cofluorescence.

35. At the time of the invention it would have been obvious to one ordinarily skilled in the art to include the energy transfer donor compound in a concentration greater than the concentration of the energy transfer acceptor macrocycle, such as a range from 1 x 10^{-5} to 1 x 10^{-3} moles per liter as Leif et al. teaches of such as concentration used for the energy transfer donor compounds (e.g. Gd) with the identical macrocyclic chelates and identical analytical methods as that of Vallarino et al.

36. At the time of the invention it would have been obvious to one ordinarily skilled in the art to vary and/or optimize the amount of fluorescence-increasing ion/energy transfer donor compound, such as a concentration range from 1 x 10^{-5} to 1 x 10^{-3} moles per liter, according to the guidance provided by Leif et al., to provide a composition having the desired properties, such as increased cofluorescence. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Conclusion

37. Claim 10 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached on 7-4 M, 7-4 T, 6 Th, 7-4 F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Melissa Perreira/
Examiner, Art Unit 1618